Remarks

Reconsideration of this Application is respectfully requested.

The specification has been amended to correct sequence identifiers and make corrections to the sequence listing. The sequence listing differs in the deletion of SEQ ID NOs:125-127 and the replacement with SEQ ID NOs:125 and 126. SEQ ID NOs:125 and 126 are identical to SEQ ID NOs:1 and 2, respectively, of priority Appl. No. 08/845,496. Appl. No. 08/845,496 was incorporated by reference in its entirety in the captioned application. Thus, the addition of SEQ ID NOs:125 and 126 in the substitute sequence listing does not constitute new matter.

In accordance with 37 C.F.R. § 1.825(b), the paper copy of the Sequence Listing and the computer readable copy of the Sequence Listing submitted herewith are the same.

Claims 38, 46, 47, 67, 68 and 69 have been amended. Support for the amendments to the claims can be found throughout the specification. Specifically, support can be found at page 108, line 5 and at page 263, line 9. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

The indefiniteness rejection

The Examiner rejected claims 24-56 under 35 U.S.C. § 112, second paragraph, for indefiniteness, for the recitation of SEQ ID NOs:125 and 126. Applicants have amended

the sequence listing. SEQ ID NO:125 is now a polynucleotide which encodes SEQ ID NO:126, a polypeptide. Accordingly, withdrawal of this rejection is respectfully requested.

The enablement rejection

The Examiner rejected claims 38-56 and 67-85 under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement. Applicants respectfully traverse this rejection.

A. As drawn to polynucleotide variants

Claim 48, from which claims 49-56 depend, is drawn to polynucleotides comprising nucleic acid sequences which are at least 95% identical to SEQ ID NO:125. Claim 77, from which claims 78-85 depend, is drawn to polynucleotides comprising nucleic acid sequences which are at least 95% identical to SEQ ID NO:1.

With respect to these claims, the Examiner states that

> [o]ne cannot extrapolate the teaching of the specification to the scope of the claims because, when given the broadest reasonable interpretation, the claims are clearly intended to encompass species of polynucleotides that encode proteins and peptides having neither structural nor functional identity with polynucleotides encoding METH1 and no guidance has been given as to how to use these species. Further, the specification has not shown that polynucleotides comprising variants of SEQ ID NO:1 or 126 are capable of functioning as that which is suggested.

Paper No. 16, page 4.

Claims 48 and 77 are not limited to polynucleotides which encode functional METH1 polypeptides. Further, claims 48 and 77 are not limited to polynucleotides which encode a polypeptide at all. The polynucleotides of claims 48 and 77 are useful as probes or primers to detect METH1 expression, regardless of whether they encode a polypeptide.

See specification, page 114, lines 14-24. Polynucleotides which are at least 95% identical to a reference polynucleotide will hybridize to the reference polynucleotide. This is due to the high degree of homology between the two polynucleotides. The polynucleotides of the claims will hybridize to the reference polynucleotides and be useful for detecting METH1 expression. Thus, Applicants have disclosed how to use all of the species of the independent claims.

In order to enable the claimed invention as required by 35 U.S.C. § 112, first paragraph, the specification need only enable a person of ordinary skill in the art to make the claimed polynucleotides and practice a single use of the claimed polynucleotides without undue experimentation. *See Raytheon Co. v. Roper Corp.*, 220 U.S.P.Q. 592 (Fed. Cir. 1983, *cert. denied*, 469 U.S. 835 (1984). Thus, the use of the polynucleotides as probes or primers is sufficient to satisfy the enablement requirement.

Assuming, *arguendo*, that the use of the polynucleotides of the invention as probes or primers is insufficient to satisfy the enablement requirements, the specification enables other uses of the polynucleotides. For example, the specification discloses, at page 231, lines 3-7, the regions of METH1 which are antigenic epitopes. Using this information, one of ordinary skill in the art would be able to make polynucleotides which encode polypeptides useful for raising METH1-specific antibodies. Methods of detecting METH1 expression using METH1 antibodies are provided in the specification at page 277, lines 23-29. Sufficient guidance is provided in the specification to make and use polynucleotides encoding epitope-containing polypeptides.

Further, Applicants have provided, throughout the specification and in particular at page 100, line 25 to page 101, line 4, and page 294, line 24 to page 296, line 14, the

functional domains and/or residues of METH1. These domains and/or residues include: the TSP domains, the metalloprotease domain, a cysteine-rich region containing two disintegrin loops, subtilisin cleavage sites, and zinc-binding sites. The locations of these domains/residues are provided in the application. One of ordinary skill in the art would know not to alter these regions in order to obtain a functional METH1 polypeptide.

Applicants have shown, at Example 4, that a recombinant construct comprising the TSP1 domain of METH1 was sufficient to suppress angiogenesis. Thus, in contrast to the Examiner's assertion, Applicants have shown that a polynucleotide encoding a variant of METH1 functions as an anti-angiogenic factor. Further, one skilled in the art would know to not alter, for example, the coding region for the TSP1 domain if an anti-angiogenic encoded polypeptide is desired.

All of the polynucleotides of the claims are useful as probes or primers. Further, one of ordinary skill in the art would be able to predict which polynucleotides of the claims are useful for raising antibodies and/or as an anti-angiogenic factor. Thus, the claims are fully enabled. Accordingly, withdrawal of this rejection is respectfully requested.

B. As drawn to polynucleotides which hybridize to SEQ ID NO:1 and SEQ ID NO:126

Claim 38, from which claims 39-45 depend, is drawn to polynucleotides which hybridize under particular conditions to a probe consisting of nucleotides 466 to 3366 of SEQ ID NO:125. Claim 69, from which claims 70-76 depend, is drawn to polynucleotides which hybridize under particular conditions to a probe consisting of nucleotides 1 to 2853 of SEQ ID NO:1.

The Examiner stated that

> the recitation of hybridization conditions is not limiting, as a smaller oligomer could hybridize under stringent conditions to the probes, as well as lengthy polynucleotides having single base mismatches within regions of homology. . . [I]t would be expected that a substantial number of the hybridizing or complementary polynucleotides encompassed by the claims would not share either structural or functional properties with polynucleotides that encode METH1 or encode proteins that have angiogenesis inhibiting properties. The specification fails to provide an enabling disclosure for how one would use such polynucleotides.

Paper No. 16, pages 5-6.

Applicants have amended the claims to specify that the polynucleotide which hybridizes to SEQ ID NO:1 or SEQ ID NO:125 is at least 30 polynucleotides in length. Thus, the claims do not encompass exceedingly small oligomers.

Applicants assert that the claims are fully enabled. One of ordinary skill in the art would be able to use all of the polynucleotides of the invention, regardless of whether or not they encode an anti-angiogenic protein. This is because all polynucleotides which hybridize to METH1 are useful for detecting METH1 expression. A single use is all that is required to satisfy the enablement requirement.

Further, as stated above in reference to the 95% identity claims, one of ordinary skill in the art would be able to predict which polynucleotides of the claims encode antigenic and/or anti-angiogenic proteins, based on the disclosure in the application. Applicants have thus enabled several uses of the polynucleotides of the claims. Accordingly, withdrawal of this rejection is respectfully requested.

C. Polynucleotides which are less than fully complementary to disclosed polynucleotides

The Examiner stated that "[c]laims 46, 47, 67 and 68 are drawn to polynucleotides which are complementary to polynucleotides encoding SEQ ID NO:2 and SEQ ID NO:125 and as such encompass polynucleotides which are complementary to fragments of the polynucleotides encoding SEQ ID NO:2 or SEQ ID NO:125." Paper No. 16, page 5.

Applicants do not agree that this is a reasonable interpretation of the claims. Nevertheless, solely to advance prosecution, Applicants have amended the claims to specify polynucleotides which are fully complementary to the recited sequences. The Examiner stated that polynucleotides which are fully complementary to the polynucleotides encoding SEQ ID NO:2 and SEQ ID NO:126 are enabled. *See* Paper No. 16, page 3. Accordingly, withdrawal of this rejection is respectfully requested.

The written description rejection

The Examiner rejected claims 38-56 and 67-85 under 35 U.S.C. § 112, first paragraph, for alleged lack of written description. Applicants respectfully traverse this rejection.

The test for the written description requirement is whether one skilled in the art could reasonably conclude that the inventor has possession of the claimed invention in the specification as filed. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563, 19 USPQ2d 1111, 1116 (Fed. Cir. 1991); M.P.E.P. § 2163.02. The Examiner bears the initial burden of presenting a *prima facie* case of unpatentability. This burden is discharged if the Examiner can present evidence or reasons why one skilled in the art would *not* reasonably conclude that Applicants possessed the subject matter as of the priority date of the present application.

In re Wertheim, 541 F.2d 257, 262, 191 USPQ2d 90, 96 (C.C.P.A. 1976); M.P.E.P. § 2163.04. In the instant case, the Examiner has not met the burden.

The Examiner states that

> the written description is not commensurate in scope with the claims drawn to polynucleotide variants having at least 95% identity to SEQ ID NO:1 and SEQ ID NO:126, isolated polynucleotides which hybridize under stringent conditions to SEQ ID NO:1 and SEQ ID NO:126, or isolated polynucleotides comprising polynucleotides which are less than fully complementary to SEQ ID NO:1 and 126 or the polynucleotides encoding SEQ ID NO:2 and SEQ ID NO:125.

Paper No. 16, page 6.

Applicants have amended claims 46, 47, 67 and 68 to more clearly specify that the polynucleotides are fully complementary to the polynucleotides encoding SEQ ID NO:2 and SEQ ID NO:126. Accordingly, by the Examiner's own admission, claims 46, 47, 67 and 68 meet the written description requirement.

Further, the Examiner states that

> the skilled artisan cannot envision the detailed structure of the encompassed polynucleotides and therefor conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation.

Paper No. 16, page 7.

Contrary to the Examiner's assertion, the skilled artisan *can* envision all polynucleotides which are at least 95% identical to SEQ ID NO:1 or SEQ ID NO:125 or hybridize to SEQ ID NO:1 or SEQ ID NO:125. Applicants have not simply provided a functional limitation for the polynucleotides of the invention, they have provided structural limitations.

The Examiner cites *University of California v. Eli Lilly and Co.*, 43 U.S.P.Q.2d 1398 (1997) as holding

> [A] generic statement which defines a genus of nucleic acids by only their functional activity does not provide an adequate written description of the genus. . . [A]n adequate written description of a DNA requires a precise definition, such as by structure, formula, chemical name, or physical properties, not a mere wish or plan for obtaining the claimed chemical invention.

Paper No. 16, page 7.

However, the present situation is distinguishable from the cited case. In *University of California*, the claims were directed to "mammalian insulin cDNA," with no structural limitation. The application disclosed the sequence of rat insulin DNA, but did not disclose the sequence of any other mammalian insulin genes.

In contrast, the present claims recite structural limitations, *i.e.*, chemical structure by identity with another polynucleotide. The specification discloses the sequence of METH1. Thus, a representative number of species is disclosed, since the chemical structure in combination with the level of skill and knowledge in the art are adequate to determine that Applicants were in possession of the claimed invention.

For the hybridization claims, one of ordinary skill in the art would not expect substantial variation among species encompassed within the scope of the claims because the highly stringent hybridization conditions set forth in the claim yield structurally similar polynucleotides. The specification discloses the full-length sequence of METH1. Thus, a representative number of species is disclosed, since highly stringent hybridization conditions in combination with the level of skill and knowledge in the art are adequate to determine that Applicants were in possession of the claimed invention.

All of the pending claims meet the written description requirement as one of ordinary skill in the art would understand that Applicants had possession of the invention at the time of filing. Accordingly, withdrawal of this rejection is respectfully requested.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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Version with markings to show changes made

The paragraph beginning on page 98, line 19, was replaced with the following:

As one of ordinary skill would appreciate, due to the possibilities of sequencing errors, as well as the variability of cleavage sites for leaders in different known proteins, the predicted METH1 polypeptide encoded by the deposited cDNA comprises about 950 amino acids, but may be anywhere in the range of 910-990 amino acids; and the predicted leader sequence of this protein is about 28 amino acids, but may be anywhere in the range of about 18 to about 38 amino acids. An alternative predicted METH1 polypeptide is shown in SEQ ID NO:126, encoded by SEQ ID NO:125, and comprises an additional 18 amino acid residues on the N-terminus. Also, the predicted METH2 polypeptide comprises about 890 amino acids, but may be anywhere in the range of 850 to about 930 amino acids; and the predicted leader sequence of this protein is about 23 amino acids, but may be anywhere in the range of about 13 to about 33 amino acids.

The paragraph beginning on page 216, line 21, was replaced with the following:

Deletion mutants of METH1 may also be made which comprise all or part of the additional sequence described in SEQ ID NO:[125]126. For example, exemplary deletion mutants include: Q-2 to S-967; R-3 to S-967; A-4 to S-967; V-5 to S-967; P-6 to S-967; E-7 to S-967; G-8 to S-967; F-9 to S-967; G-10 to S-967; R-11 to S-976; R-12 to S-967; K-13 to S-967; L-14 to S-967; G-15 to S-967; S-16 to S-967; D-17 to S-967; and M-18 to S-967.

The sequence listing was replaced.

The claims were amended as follows.

38. (once amended) An isolated polynucleotide at least 30 nucleotides in length which hybridizes at 42°C in 50% formamide, 5xSSC, 50 mM sodium phosphate, 5x Denhardt's solution, 10% dextran sulfate, and 20 μg/ml denatured, sheared salmon sperm DNA, followed by washing in 0.1xSSC at 65°C, with a probe consisting of nucleotides 466 to 3366 of SEQ ID NO:125.

46. (once amended) An isolated polynucleotide comprising a nucleotide sequence which is fully complementary to a polynucleotide sequence encoding amino acids 1 to 967 of SEQ ID NO:126.

47. (once amended) The isolated polynucleotide of claim 46, comprising a nucleotide sequence which is fully complementary to nucleotides of 466 to 3366 SEQ ID NO:125.

67. (once amended) An isolated polynucleotide comprising a nucleotide sequence which is fully complementary to a polynucleotide sequence encoding amino acids 1 to 950 of SEQ ID NO:2.

68. (once amended) The isolated polynucleotide of claim 67, comprising a nucleotide sequence which is fully complementary to nucleotides 1 to 2853 of SEQ ID NO:1.

69. (once amended) An isolated polynucleotide at least 30 nucleotides in length which hybridizes at 42°C in 50% formamide, 5xSSC, 50 mM sodium phosphate, 5x Denhardt's solution, 10% dextran sulfate, and 20 μg/ml denatured, sheared salmon sperm DNA, followed by washing in 0.1xSSC at 65°C, with a probe consisting of nucleotides 1 to 2853 of SEQ ID NO:1.